

Continuing Medical Education (CME) articles

Advances in Neoadjuvant and Adjuvant Immunotherapy and Targeted Therapy for Resectable NSCLC

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Resectable non-small cell lung cancer (NSCLC) is currently treated with cisplatin-based adjuvant chemotherapy following surgical resection. Despite treatment with curative intent, there are high rates of disease recurrence with distant metastases, resulting in a 5-year mortality of 20-60%. Advances in immunotherapy (IO) in stage III and IV have led to improvements in overall survival. Our article reviews important studies utilizing IO in both the neoadjuvant and adjuvant settings for resectable NSCLC. We highlight the results of two phase III randomized studies, Checkmate 816 for neoadjuvant therapy and IMpower 010 for adjuvant therapy. If clinically meaningful event-free survival benefit is observed, Checkmate 816 will likely lead to the first FDA approved regimen for neoadjuvant chemoimmunotherapy in resectable NSCLC. IMpower 010 has led to the FDA approval of adjuvant atezolizumab for resected NSCLC with PD-L1 \geq 1%. We provide our insight into how the results of these studies should be applied clinically. We also discuss the data and current indications for the use of targeted molecular therapy, including the results of the ADAURA trial for adjuvant osimertinib. We conclude by discussing future considerations.

HIGHLIGHTS

- **Despite surgical resection and adjuvant chemotherapy, there is a high rate of disease recurrence and mortality in resectable NSCLC. Numerous studies are investigating the use of IO as neoadjuvant and adjuvant modalities of treatment.**
- **Overall survival is the most important determinant of efficacy, but other endpoints such as pathologic complete response (pCR) and major pathologic response (MPR) are used as surrogates in neoadjuvant trials**
- **Checkmate 816 investigated use of nivolumab with platinum-doublet therapy, revealing increased rates of pCR with reported improvements in yet to be published data for event-free survival (EFS).**
- **IMpower 010 has led to FDA approval for adjuvant atezolizumab in PD-L1 positive resectable NSCLC.**
- **ADAURA revealed significant disease-free survival (DFS) benefit for adjuvant osimertinib in EGFR mutated resected stage II-III NSCLC, leading to FDA approval**
- **Future studies should focus on patient selection for either adjuvant or neoadjuvant therapy, role of IO alone, length of adjuvant treatment, and the role of circulating tumor DNA (ctDNA).**

INTRODUCTION

Lung cancer is one of the most diagnosed cancers worldwide with an estimated 2 million new cases annually and 1.76 million deaths per year.¹ Approximately 85% of lung cancers are non-small cell lung cancers (NSCLC) in histology.¹ The mainstay of treatment for localized NSCLC is surgical resection, when possible, offering the best chance of cure.^{2,3} In the mid-2000s, adjuvant cisplatin-based chemotherapy following surgery was found to increase overall survival (OS) from 4-8% compared to surgery alone, offering a modest survival benefit for curative intent therapy.⁴⁻⁷ Despite improved outcomes with adjuvant chemotherapy, 20-60% of patients die within 5 years with 20% of patients in stage I, 50% of patients in stage II, and 60% of patients with stage IIIA.⁸ Moreover, the risk for distant disease recurrence is high, accounting for approximately half of all recurrences.^{9,10} Prior efforts to improve overall survival through the addition of bevacizumab to adjuvant chemotherapy found no benefit.¹¹ The combination of surgery and adjuvant chemotherapy continues to be the standard treatment for resectable NSCLC. Treatment and outcome survival for metastatic NSCLC has improved with advances in immunotherapy (IO) and targeted-molecular therapy. Given the high risk of death following definitive treatment, along with multiple treatment advancements in thoracic oncology, there is demand for improved treatments in resectable NSCLC. We review the literature involving immunotherapy in the adjuvant and neoadjuvant setting. We will also review the use of targeted molecular therapy in this patient population.

IMMUNOTHERAPY

Anti-PD-1/PD-L1 and anti-CTLA-4 therapies are now used in front-line treatment for metastatic NSCLC with improved survival compared to chemotherapy alone. Pembrolizumab in combination with platinum-doublet chemotherapy or alone for PD-L1 \geq 50% have increased OS by 15-20% compared to chemotherapy alone.¹²⁻¹⁴ The combination of nivolumab and ipilimumab demonstrated a 2-year OS benefit of 10% compared to chemotherapy.^{15,16} Consolidative immunotherapy with durvalumab for 1 year following concurrent chemoradiotherapy for non-resectable stage III NSCLC has demonstrated a 5-year survival benefit of 10%.¹⁷ These improvements in survival in later-stage disease have provided an impetus for investigating their utility in early stages. There are multiple studies underway investigating the use of these agents in both the adjuvant and neoadjuvant setting for resectable NSCLC. We will discuss the current evidence for use of IO in these settings.

NEOADJUVANT IMMUNOTHERAPY

The role of neoadjuvant therapy with traditional chemotherapy has been established in multiple solid tumor subtypes, including breast, colorectal, head and neck, and bladder cancers. Two main theoretical advantages to neoadjuvant therapy include greater organ preservation by decreasing the size of the surgical field along with treatment of micrometastatic disease. This allows for earlier treatment of localized disease not possible in the setting of poor surgical recovery. Disadvantages include treatment toxicity and delaying definitive surgery, leading to disease progression where curative treatment is not possible.

In the context of NSCLC, a meta-analysis of 15 randomized-controlled trials found an OS benefit of 5% at 5 years with neoadjuvant chemotherapy compared to surgery alone in patients with stage IB-IIIa disease.¹⁸ A systematic review of 32 trials found no difference in overall and disease-free survivals between neoadjuvant and adjuvant chemotherapy.¹⁹ This led to neoadjuvant therapy being offered in select circumstances to convert borderline unresectable disease into resectable tumors, as well as patients with a high risk of metastatic disease, but not clinically detected. For resectable tumors, neoadjuvant chemotherapy is not favored given the lack of OS benefit.

The mechanism of cytotoxic chemotherapy differs from immunotherapy. While chemotherapy directly affects tumor cells, PD-1/PD-L1 inhibition allows for immune-mediated stimulation of host T-cells through antigen presentation by tumors. This leads to the release of cytokines, stimulating further immune cell activation and tumor cell death. A higher antigen burden could lead to greater immune cell activation. Therefore, neoadjuvant IO could provide greater efficacy than adjuvant use, leading to improved survival. Disadvantages to neoadjuvant IO include delay of definitive treatment due to adverse reactions, leading to disease progression. Additionally, there have been anecdotal reports of increased fibrosis and adhesions associated with neoadjuvant immunotherapy.²⁰ This could lead to complications with surgical resection and poor wound heal-

ing.

Preclinical trials have shown promising results with neoadjuvant IO. Liu et al.²¹ investigated the use of neoadjuvant and adjuvant anti-PD-1 following primary tumor resection in mice models of metastatic triple-negative breast cancer. In the neoadjuvant arm, 95% of mice compared to 25% in the control arm were alive 250 days from study initiation. In addition, neoadjuvant therapy resulted in a statistically significant higher concentration of circulating CD-8 positive tumor-specific T-cells. Cascone et al.²² investigated outcomes in mice implanted with NSCLC cells treated with neoadjuvant anti-PD-1, anti-CTLA-4, a combination of anti-PD-1/CTLA-4, or observation. Postoperatively, mice in the observation arm received 3 cycles of anti-PD-1, anti-CTLA-4, or PD-1/CTLA-4 combination. Mice treated with neoadjuvant combination therapy were found to live significantly longer compared to adjuvant therapy or neoadjuvant monotherapy.

Before reviewing clinical trials, it is important to understand the endpoints used. The primary objective of IO in resectable NSCLC is to increase survival. Hence, the most important endpoint is OS. Using OS as the primary endpoint presents logistical challenges. Many patients must be accrued to meet demands for statistical power to ascertain survival differences between study arms. Moreover, it could take years to identify differences in OS. Not only does this delay drug development, but precludes patients receiving life-saving therapy while OS data matures. This necessitates the need for surrogate endpoints. Immunotherapy studies in the metastatic setting demonstrate early benefits in progression-free survival (PFS) translated to sustained benefits in OS.²³ This led to the earlier incorporation of IO in the treatment of metastatic lung cancer. A meta-analysis of 20 studies of resectable and locally advanced NSCLC found a high correlation between PFS and disease-free survival (DFS) with OS.²⁴ PFS and DFS are established as surrogates for OS in studies investigating cytotoxic chemotherapy. Currently, there is no data confirming this relationship for studies investigating IO or targeted therapy. Realizing this limitation, PFS and DFS may be used as endpoints until further OS matures. Multiple studies have noted an association between histologic response to neoadjuvant therapy and prognosis.²⁵⁻²⁷ This led to the use of pathologic complete response (pCR) as another surrogate for OS. Major pathologic response (MPR), defined as less than or equal to 10% viable tumor cells in a resected specimen, has been recommended by the International Association for the Study of Lung Cancer (IASLC) as the primary endpoint in neoadjuvant studies.²⁸ MPR is a more clinically achievable endpoint than pCR and has been found to be associated with OS in neoadjuvant therapy.²⁹ Many studies, however, were designed prior to this formal recommendation. Most studies include MPR or pCR as one of the primary endpoints. The main challenge of these two endpoints is the variation of pathology review. Disease-free survival is often included as a surrogate endpoint of OS, due to its objectivity and clinical significance.

One of the earliest clinical studies was conducted by Forde et al.³⁰ This single-arm study examined the use of 2 cycles of neoadjuvant nivolumab for stage IA-IIIa NSCLC. Twenty of 22 patients underwent 2 cycles of neoadjuvant

Table 1. Ongoing Trials with Neoadjuvant Immunotherapy

NCT	Regimen	Primary Endpoint	Stage	Phase
NCT04047186	Nivolumab+S	MPR	Multi-GGO	2
NCT02818920 TOP 1501	Pembrolizumab+S+Pembrolizumab	Feasibility and safety	Ib-IIIa	2
NCT03197467 NEOMUN	Pembrolizumab+S	Feasibility and safety	II-IIIa	2
NCT02994576 PRINCEPS	Atezolizumab+S	Feasibility and safety	Ib-IIIa	2
NCT03030131 IONESCO	Durvalumab+S	R0 surgical resection	Ib-IIIb	2
NCT04371796	Sintilimab+S	MPR	II-IIIa	2
NCT03217071 PembroX	Pembrolizumab+S (Pembrolizumab+RT)+S (Durvalumab+RT)+S	Δ TILs	I-IIIa	2
NCT03237377	(Durvalumab+RT)+S (Durvalumab+Tremelimumab+RT)+S	Feasibility and safety	IIIa	2
NCT02904954	Durvalumab+S+Durvalumab*1y (Durvalumab*3+RT)+S+Durvalumab*1y	MPR	I-IIIa	2

MPR: main pathological response, S: surgery, TIL: tumor infiltrating lymphocyte, RT: radiation therapy.

treatment. MPR was found in 9 of 20 patients (45%; 95% confidence interval [CI]: 23–68). The median time interval from 2nd nivolumab dose to surgery was 18 days, with no significant delay in surgery. Immune-related adverse events (irAEs) occurred in 5 patients with one patient having grade 3 pneumonia and no grade 4-5 events were noted.

Combination neoadjuvant immunotherapy has been investigated by Cascone et al in the NEOSTAR trial.³¹ This phase 2 trial randomized 44 patients with stage IA-IIIa to either 3 cycles of single-agent nivolumab or combination with ipilimumab prior to surgery. Thirty-nine patients underwent curative surgery, with 1 patient having progressive disease. MPR rate was 24% (5/21, 95% CI = 8–47%) and 50% (8/16, 95% CI = 25–75%) for the nivolumab and nivolumab/ipilimumab groups respectively. pCR was noted for 6 patients in nivolumab/ipilimumab compared to 2 with nivolumab alone. Given the small sample size, no definitive conclusions can be made, but the results warrant further investigation through larger randomized trials.

Given the success of chemoimmunotherapy in the metastatic setting, this has also been investigated in neoadjuvant treatment by Provencio et al.³² Three cycles of neoadjuvant nivolumab combined with paclitaxel and carboplatin was given to 46 patients with stage IIIa NSCLC. Following surgery, patients received adjuvant nivolumab for 1 year. Forty-one of 46 patients underwent resection. No significant delays in surgery were observed. Seventy-one percent of patients (24) achieved pCR with 83% (34) achieving MPR. At 24 months, PFS was noted to be 77.1%. Multiple ongoing trials are investigating the use of neoadjuvant IO alone (Table 1) and chemoimmunotherapy combinations (Table 2).

During ASCO 2021, results of the first phase 3 neoadjuvant trial were presented.³³ Checkmate 816 enrolled 358 patients with stage IB-IIIa randomized to 3 cycles of

nivolumab plus investigator's choice of platinum-doublet chemotherapy or platinum-doublet chemotherapy alone. Primary endpoints included event-free survival (EFS) and pCR. A comparable number of patients in both study arms proceeded to definitive surgery. Disease progression prior to surgery was observed in 12 of 149 patients in the nivolumab/chemotherapy and 17 of 137 patients in the chemotherapy group. pCR rates were 24% and 2.2% in the nivolumab/chemotherapy and chemotherapy treatment arms respectively, which was statistically significant across all stages. MPR in the nivolumab/chemotherapy arms was 36.9% and 8.9% with chemotherapy alone. Pneumonectomy was performed in 25% of patients in the chemotherapy group as opposed to 17% in the nivolumab/chemotherapy group. Data regarding EFS have not formally been reported, but recent press releases suggest an EFS advantage with neoadjuvant nivolumab.

In summary, the role of neoadjuvant immunotherapy in resectable NSCLC is an area of active research. Many initial trials revealed encouraging results, but definitive conclusions were difficult to make given smaller sample sizes. Checkmate 816 is the first randomized phase 3 revealing a statistically significant benefit in MPR and pCR. It is likely other ongoing phase 3 trials will reveal similar results. Should these findings lead to an increased DFS, and eventually survival, the use of neoadjuvant chemoimmunotherapy will likely become part of the treatment for resectable NSCLC. If clinically meaningful EFS benefit is confirmed, it is reasonable to recommend neoadjuvant chemoimmunotherapy while OS data matures.

ADJUVANT IMMUNOTHERAPY

The current standard of care for resectable NSCLC involves adjuvant chemotherapy. Adjuvant therapy allows for earlier

Table 2. Neoadjuvant Chemoimmunotherapy combinations

NCT	Regimen	Primary Endpoint	Stage	Phase
NCT04541251	(Camrelizumab+CT)*3	MPR	Ib-IIIa	2
NCT04144608	(Toripalimab+CT)+S	R0 surgical resection	IIIa or IIIb	2
NCT04304248 NeoTAP01	(Toripalimab+CT)*3+S	MPR	IIIa or IIIb	2
NCT04586465 DYNAPET	(Pembrolizumab+CT)*3+S	MPR SUV	IIa-IIIb	2
NCT04379739	Camrelizumab+CT+S Camrelizumab +Apatinib+S	MPR	II-IIIa	2
NCT04865705	Tislelizumab + CT	R0 surgical resection	IIIa or IIIb	2
NCT04512430 Neo-DIANA	Atezolizumab+Bevacizumab+CT)+S+ (Atezolizumab q4w*6 mon)	MPR	IIIa (EGFR+)	2
NCT04326153	(Sintilimab+CT)+S+(Sintilimab*8+CT* 2)	2yr-DFS	IIIa	2
NCT03838159 NADIM-II	(Nivolumab +CT)*3+S+(Nivolumab*1 y)	pCR	IIIa or IIIb	2
NCT04338620	(Camrelizumab+CT)+S NAC+S	pCR	IIIa or IIIb (IIIb limited to T3N2)	2
NCT04422392	(ICI+CT)+S+(ICI+CT) NAC+S+CT	24-month PFS	IIIa (N2 only)	2
NCT04061590	Pembrolizumab +S (Pembrolizumab+CT)+S	Proportion of TILs	I-IIIa	2
NCT04459611 neoSCORE	(Sintilimab+CT)*2+S+(CT*2+Sintilimab*1y) (Sintilimab+CT)*3+S+(CT*1+Sintilimab*1y)	MPR	I-IIIa	2
NCT03916627	Cemiplimab+S+(Cemiplimab+CT) (Cemiplimab+CT)+S+(Cemiplimab+CT) NAC+S+(Cemiplimab+CT)	MPR	NSCLC	2
NCT04245514 SAKK 16/18	Durvalumab*1+CT*3+RT)+S+ (Durvalumab*13q4w)	12-month EFS	T1-4 (>7 cm) N2	2
NCT04465968 DEEP_OCEAN	(Durvalumab+RT+CT)+S+Durvalumab (Durvalumab+RT+CT)+Durvalumab	3-OS	III	3
NCT04379635	(Tislelizumab 200mg Q3W +CT)*3+S+(Tislelizumab 400mg Q6W)*8 Placebo+CT+S+Placebo	MPR EFS	II-IIIa	3
NCT03425643 KEYNOTE-671	(Pembrolizumab+CT)*4+S+(Pembrolizumab*1y) (NAC+Placebo)+S+Placebo	EFS OS	II-IIIb (N2)	3
NCT03456063 IMpower030	(Atezolizumab+CT)+S+(Atezolizumab*16) Placebo+NAC+S+Placebo	EFS	II-IIIb (T3N2)	3
NCT03800134 AEGEAN	(Durvalumab+CT)+S NAC+S	pCR EFS	II-IIIb (N2)	3
NCT04025879	(Nivolumab+CT)+S+(Nivolumab) Placebo+NAC+S+Placebo	EFS	II-IIIb (T3N2)	3

NSCLC: Non-small cell lung cancer, MPR: main pathological response, pCR: pathological complete response, ICI: immune checkpoint inhibitor, S: surgery, CT: chemotherapy, OS: overall survival, PFS: progressive free survival, EFS: event-free survival, TIL: tumor infiltrating lymphocyte, RCT: randomized controlled trial, RT: radiation therapy.

definitive surgical intervention. This avoids treatment-related complications from neoadjuvant therapy, delaying time to surgery. Given the lack of survival benefit between adjuvant and neoadjuvant chemotherapy, most clinicians prefer to initiate definitive therapy upfront. Concerns with IO in the neoadjuvant and adjuvant settings remain unanswered. Adjuvant IO could allow for sustained immunologic

response to any residual microscopic disease following surgery. The use of adjuvant IO in resectable NSCLC with or without standard chemotherapy is currently being investigated by several ongoing trials summarized in [Table 3](#). The first phase 3 trial demonstrating the benefit of adjuvant immunotherapy is IMpower 010.³⁴

Table 3. Trials with adjuvant immunotherapy in resectable NSCLC

Trial	Stage	Intervention after surgery	Estimated enrollment	Primary endpoint
ANVIL	IB-III A	Arm A: optional CT and RT nivolumab 1 year Arm B: optional CT and RT → observation	903	DFS OS
PEARLS/KEYNOTE-091	IB-III A	Arm A: optional CT → pembrolizumab 1 year Arm B: optional CT → placebo	1080	DFS
BR31	IB-III A	Arm A: optional CT (+ optional RT if N2) → durvalumab 1 year Arm B: optional CT (+ optional RT if N2) → placebo	1360	DFS
ALCHEMIST	IB-III A	Arm A: CT Arm B: CT + pembrolizumab Arm C: CT + pembrolizumab → pembrolizumab	1263	DFS OS
MEMAID-1	II-III A	Arm A: Durvalumab + CT for MRD (+) Arm B: Placebo + CT for MRD (+)	332	DFS
MERMAID-2	II-III A	Arm A: Durvalumab for MRD (+) after CT Arm B: Placebo for MRD (+) after CT	284	DFS for PD-L1 ≥ 1%

OS: overall survival, DFS: disease-free survival, RT: radiotherapy, CT: chemotherapy

IMpower 010 randomized 1005 patients with stage IB-III A to 21 cycles of atezolizumab or placebo following resection and adjuvant platinum-doublet chemotherapy. The primary endpoint was DFS assessed in stage II-III A with PD-L1 positivity ($\geq 1\%$ per SP263 assay), stage II-III A regardless of PD-L1 expression, and all randomized stage IB-III A (ITT population). In stage II-III PD-L1 positive patients, median DFS was not reached in the atezolizumab arm compared with 35.3 months in the placebo arm (HR 0.66; 95% CI: 0.50, 0.88; $p=0.004$). For all stage II-III patients, median DFS was 42.3 months with atezolizumab compared to 35.3 months with placebo (HR 0.79; 95% CI: 0.64, 0.96; $p=0.02$). For patients in the ITT population, no statistically significant difference in median DFS was noted when patients with stage IB were included (HR 0.81; 95% CI: 0.67, 0.99; $p=0.04$). Overall survival was not formally tested in the ITT population due to not meeting statistical significance for DFS with the hierarchical design of the study. Data for OS has not been finalized. Based on these findings, atezolizumab is now FDA approved in the adjuvant setting for stage II-III resected NSCLC with PD-L1 $\geq 1\%$ following platinum-doublet chemotherapy.

How should data from IMpower 010 be applied? Although patients with sensitizing *EGFR* or *ALK* mutations were not excluded, prior data suggests patients with *EGFR* mutations derive lower clinical benefit with immunotherapy.^{35,36} Patients treated with tyrosine kinase inhibitors (TKIs) following immunotherapy also had higher rates of irAEs. Therefore, those with sensitizing driver mutations should be treated with targeted therapy, specifically for *EGFR* mutated cancers, which will be addressed in the next section. For PD-L1 negative patients, no benefit in DFS was observed. Therefore, adjuvant immunotherapy would not be recommended. These patients could be treated with standard chemotherapy or enrolled in a clinical trial. A pre-specified subset analysis of patients with PD-L1 $\geq 50\%$ revealed a 57% reduction in risk of progression or death (DFS HR 0.43; 95% CI: 0.27, 0.68). This benefit was not seen in a subset of patients with PD-L1 $\geq 1-49\%$ (DFS HR 0.87; 95% CI: 0.60, 1.26). We would strongly recommend adjuvant IO

for patients with PD-L1 $\geq 50\%$. Although this same benefit was not observed in the 1-49% subset, shared planning should be conducted on an individual basis, discussing risks, benefits, as well as patient preferences. PD-L1 is a dynamic marker, with expression changing over time in up to one third of patients, particularly after chemotherapy.³⁷ It is possible patients could become more sensitive to immunotherapy. This raises the question of utilizing IO alone as opposed to combination with chemotherapy. MERMAID-1 and MERMAID-2 are phase III randomized trials assessing the efficacy of durvalumab alone and durvalumab/chemotherapy only for patients found to have minimal residual disease (MRD) by circulating tumor DNA (ctDNA). This could lead to further trials utilizing ctDNA to assess which patients would benefit from adjuvant treatment.

TARGETED THERAPY

Following the approval of erlotinib in 2013 for the front-line treatment of *EGFR* mutated metastatic NSCLC,³⁸ therapies targeting multiple oncogenic driver mutations have been approved. Sotorasib for *KRAS* p.G12C³⁹ and amivantamab for *EGFR* exon 20 insertion mutation⁴⁰ are the newest targeted therapies for metastatic NSCLC. Given the efficacy of *EGFR* tyrosine kinase inhibitor (TKI) therapy in metastatic disease, subsequent trials investigated use for adjuvant treatment. Initial studies of adjuvant first-generation *EGFR* TKIs did not demonstrate a significant survival benefit. Goss et al found no DFS or OS benefit for gefitinib in stage IB-III A resected NSCLC.⁴¹ Only 4% of patients had confirmed *EGFR* mutation. The RADIANT trial⁴² for stage IB-III A noted a DFS benefit but was not found to be statistically significant. *EGFR* expression was noted in 17% of patients by IHC or FISH. The CTONG1104 trial⁴³ comparing adjuvant gefitinib to cisplatin-based chemotherapy in patients with stage II-III A (N1-N2) found a DFS benefit, but not increased survival. All patients had sensitizing *EGFR* mutations per PCR. [Table 4](#) summarizes the adjuvant *EGFR* TKI studies.

Table 4. Trials investigating adjuvant EGFR inhibition

Study	Phase, study design, and sample size	Stage	EGFR mutation status	aCT, % receiving aCT	Treatment regimen	Primary end points	Median follow-up (years)	Outcome
BR 19	Phase 3, randomized, double-masked, placebo controlled (n=503)	IB-III A	Wild type and mutated, only 15 patients with mutation	Optional, 17%	Gefitinib vs placebo for 2 years	DFS, OS	4.7	No difference in DFS or OS; EGFR mutation not prognostic
RADIANT	Phase 3, randomized, double-masked, placebo controlled (n=973)	IB-III A	Positive by IHC or FISH, 161 with sensitizing mutation	Optional, 52.9%	Erlotinib vs placebo for 2 years	DFS	3.9	No difference in DFS, OS data immature. No difference in DFS in EGFRm subset
SELECT	Phase 2, single-arm, open-label (n=100)	IA-III A	All with sensitizing mutation	As per staging, not reported	Erlotinib for 2 years	2-year DFS	5.2	2-year DFS 88%
CTONG1104	Phase 3, randomized, open-label (n=222)	II-III A	All with sensitizing mutation	Offered to chemotherapy arm, 50%	Cisplatin+Vinorelbine for 4 cycles vs gefitinib for 2 years	DFS	6.4	DFS longer in gefitinib arm, no difference in OS
ADAURA	Phase 3, randomized, double-masked, placebo controlled (n=682)	IB-III A	All with sensitizing mutation	Optional, 60%	Osimertinib vs placebo for 3 years	DFS for stage II-III	1.84 for osimertinib, 1.24 for placebo	2-year DFS 90% in osimertinib arm vs 44% in placebo arm

aCT: adjuvant chemotherapy, DFS: disease-free survival, EGFRm: EGFR mutant, FISH: Fluorescence in situ hybridization, IHC: immunohistochemistry, OS: overall survival

Third-generation *EGFR* TKI osimertinib demonstrated significantly improved OS in previously untreated metastatic *EGFR* mutated NSCLC compared to 1st or 2nd generation TKIs in the FLAURA trial.⁴⁴ Subsequently, its efficacy in the adjuvant setting was tested in the ADAURA trial.⁴⁵ This phase 3, double-masked, placebo-controlled trial randomized 682 patients with stage IB-IIIa resected NSCLC to placebo or osimertinib for 3 years following adjuvant chemotherapy. The primary endpoint was DFS in stage II-IIIa with OS as a secondary endpoint. At 24 months, DFS for stage II-IIIa patients was 90% in the osimertinib arm compared to 44% for the placebo arm (HR=0.17; 99% CI: 0.11-0.26; p< 0.001). When stage IB was included, DFS at 24 months was 89% in the osimertinib arm compared to 52% in the placebo arm (HR=0.20; 99% CI: 0.14-0.30; p<0.001). Based on these results, the treatment arms were unmasked at an interim analysis. OS data were immature at the time of the interim analysis. Osimertinib was FDA approved for adjuvant therapy in *EGFR* mutated stage IB-IIIa NSCLC on December 18th, 2020. While approval for adjuvant Osimertinib was based on the significant improvement in DFS, it will be necessary to follow up on OS data. Similar encouraging improvements in DFS were observed in the CTONG1104 trial, but did not lead to improvement in OS, which is the gold standard for treatment with curative intent. Given the magnitude to which osimertinib improved DFS, we would favor adjuvant treatment with osimertinib.

Osimertinib in the neoadjuvant setting with chemotherapy is being investigated in the ongoing NeoADAURA trial (NCT04351555). The rationale for combining osimertinib and chemotherapy comes from preclinical data suggesting delayed onset to osimertinib resistance and greater tumor cell death.⁴⁶ Another trial is underway to help screen patients for targeted therapy.⁴⁷ Trials with *ALK* mutated resectable NSCLC are investigating the use of targeted therapy in the neoadjuvant and adjuvant settings (ALCHEMIST, NCT02201992; ALENO, NCT05015010). The use of targeted agents for both neoadjuvant and adjuvant treatment in *ALK*, *ROS-1*, *NTRK*, *BRAF V600*, and *RET* is also ongoing (NCT04302025). These and other future trials will help clarify the role of targeted therapy in resectable NSCLC.

CONCLUSION

Improved outcomes for resectable NSCLC are an area of unmet need. With improved survival for metastatic and locally advanced disease with immunotherapy and targeted molecular therapy, research has focused on utilizing these approaches for resectable NSCLC. In the neoadjuvant setting, multiple phase II trials demonstrated encouraging results, but Checkmate 816 is the first phase III randomized trial revealing significantly improved pCR rates with the addition of immunotherapy. Early reports suggest the improvement in pCR is associated with improvement in EFS. If confirmed, these findings could lead to FDA approval of neoadjuvant nivolumab in combination with platinum-doublet therapy. Even if approved, a confirmed benefit in OS is needed to justify the neoadjuvant chemo-IO approach. IMpower 010 and ADAURA trials both have FDA approval and are currently recommended for adjuvant treatment of PD-L1 positive and *EGFR* mutated resected NSCLC. While these recommenda-

tions are based on significant improvements in DFS, definitive OS benefit is required to justify associated costs and potential treatment toxicities. In other words, recurrence must be prevented and not simply delayed.

FUTURE DIRECTIONS

The studies highlighted in this article reveal promising inroads to improving survival in resectable NSCLC. Despite advancements in knowledge, many questions remain unanswered. While Checkmate 816 used combination chemo-IO, it remains to be seen whether there is a role for IO therapy alone in the neoadjuvant setting. This could avoid the toxicity from platinum-doublet chemotherapy and allow for neoadjuvant therapy for those who are not candidates for chemotherapy. There are no active phase III trials investigating this important clinical question. Which patients derive the most benefit from a neoadjuvant chemoimmunotherapy approach? Could more patients with N2 nodal disease with resectable primary tumors become surgical candidates following neoadjuvant chemoimmunotherapy? Theoretically, this seems possible, but can only be answered through clinical trials. If additional neoadjuvant chemoimmunotherapy regimens are approved, which regimen would be preferred? While this could be tailored based on the side effect profile on an individual basis, there would be questions of whether one regimen is superior. These questions should be addressed with future studies.

With regards to adjuvant therapy, the duration of immunotherapy is yet to be determined. Patients in PACIFIC and KEYNOTE-407 trials for locally advanced and metastatic disease used 1 and 2 years of immunotherapy. Patients in IMpower 010 and ADAURA trials received adjuvant treatment for 1 and 3 years respectively. No biologic rationale for the length of treatment has been provided. More data could be obtained on different durations of treatment and their impact on OS. If longer treatment durations do not lead to longer survival, then patients could be spared potential treatment toxicity. With the growing body of evidence suggesting a role for IO in both the neoadjuvant and adjuvant settings, it will be necessary to decide how to utilize which approach. Is neoadjuvant immunotherapy (either alone or in combination with chemotherapy) superior to adjuvant immunotherapy? It could be possible that a combined neoadjuvant approach is superior to either approach alone. With the advent of liquid biopsies, we may be able to select for patients requiring adjuvant immunotherapy, avoiding treatment-related toxicities. The answer to these questions should guide future clinical trials.

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